COMPLETE AND PARTIAL PERFUSION OF ANIMAL AND HUMAN SUBJECTS WITH THE PUMP-OXYGENATOR

A Study of Factors Yielding Consistent Survival. Successful Application to One Case

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THE field of cardiac surgery has advanced rapidly in the past sixteen years, and the limits of possible intervention continue to enlarge. The types of intracardiac congenital deformity which still defy consistently successful surgical correction are, in general, those which require a dry field in an open heart for periods longer than can be provided by refrigeration and occlusion of the venae cavae.

The development of a pump-oxygenator apparatus to by-pass the heart and thus to achieve this end was first undertaken by Gibbon[1] in 1937. The group in this laboratory has studied the problem since 1947. Report of application to a clinical case was made in 1951.[2] In 1952 some of us reported metabolic and other changes associated with use of such an apparatus in dogs.[3] One of the important factors was the frequency of blood stream contamination with the apparatus then employed.

The group therefore designed and constructed an improved pump-oxygenator which could be autoclaved after full assembly. During 1953 and early 1954 perfusions were run in dogs for evaluation of this apparatus, and it was concluded that air embolization was a major problem. From July 1,

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1953, to July 1, 1954, sixty-two perfusions produced only twenty survivors. A return to the earlier apparatus revealed that it also frequently permitted air embolization, although often without lethal effect.

Studies of Geoghegan and Lam[4] showed that air embolization to the coronary arteries can be reversible, but that much embolization to the cerebral vessels is usually lethal. This laboratory therefore concentrated on the effects of intracarotid air embolism and established the nature of the lesions produced, the tolerance of dogs to varying flows, and the methods of detection of air embolism of degree sufficient to be lethal but not sufficient to be detected at autopsy. (Surgical Forum, Nov. 26, 1954.)

The apparatus herein described was therefore developed to eliminate air embolism, and after several years of work we have evolved a safe and efficient technique for extracorporeal circulation. The basic premises have not changed. The apparatus must furnish an adequate amount of oxygenated blood under adequate pressure without introducing air emboli or causing hemolysis.

During the development stage, July to October, 1954, twenty-five total perfusions were performed; eleven dogs survived. From Nov. 28, 1954, to Feb. 5, 1955, there were twenty-four total perfusions with twenty-one survivors, the three deaths being due to other factors than the pump-oxygenator.

An analysis of the data from dogs perfused unsuccessfully in the past has convinced us that there were two primary causes of death: air embolism during perfusion and hemorrhage during the first twelve hours after perfusion. It has been apparent from the reports of other workers that these problems have not been peculiar to this laboratory.[5-9]

METHODS

Mongrel dogs, weighing 10 to 30 kilograms, are anesthetized with intravenous pentobarbital sodium. The chest is opened through the bed of the right fifth rib, or occasionally through a long incision through both fourth intercostal spaces which transects the sternum. The azygos vein is ligated, and sling ligatures are placed around both venae cavae close to the right atrium. The right external jugular vein is exposed in the neck, and the right and left femoral arteries and veins are exposed at the groin. Electrocoagulation of even the tiniest bleeding points is essential. Two and one-half milligrams of heparin per kilogram body weight is given intravenously after all dissection has been completed.

The method of collecting venous blood has passed through several phases. Originally[10] one cannula was passed through the azygos vein into the superior vena cava and a second cannula was passed through the right atrial appendage into the inferior vena cava. These cannulas interfered with the surgeon's access to the heart. The second method used a single catheter passed centrally through one external jugular. There were fenestrations above and below the right atrium to drain the superior and inferior venae cavae. At present, separate cannulas of 5 mm. diameter polyethylene tubing are introduced via an external jugular vein into the superior vena cava and via a femoral vein into the inferior vena cava. Sling ligatures of umbilical tape around the superior vena cava, inferior vena cava, and the outflow tracts of both ventricles permit exclusion of the heart and lungs from the circulation. Provision of a vent in the apex of the left ventricle, as suggested by Gibbon,[11] has permitted omission of outflow occlusion. Blood extruded through this vent by contraction of the left ventricle is returned by gravity to the oxygenator circuit. Air will not be embolized, when the left heart has been opened, if the pressure in the left ventricle is thus continuously maintained below that maintained in the aorta by the perfusion apparatus.

An electromagnetically recording rotameter, patterned after that of Senning,[12] measures the venous flow from animal to oxygenator.

Blood is filmed on the revolving disks of the oxygenator previously described from this laboratory.[2] Two to four disks, 50 cm. in diameter made of 18 by 18 wire mesh, are rotated in a horizontal axis at 24 r.p.m. Although oxygen containing 3 per cent CO_2 was used earlier, at present a stream of 100 per cent O_2 at 11 L. per minute passes through the oxygenator. Each disk is capable of raising the O_2 saturation of normal blood from 50 per cent to 95 per cent at a rate of about 500 c.c. per minute.

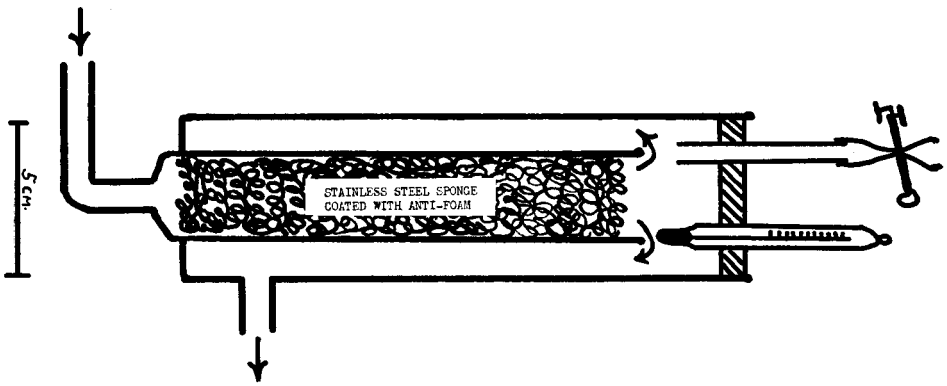

Fig. 1.—Bubble trap.

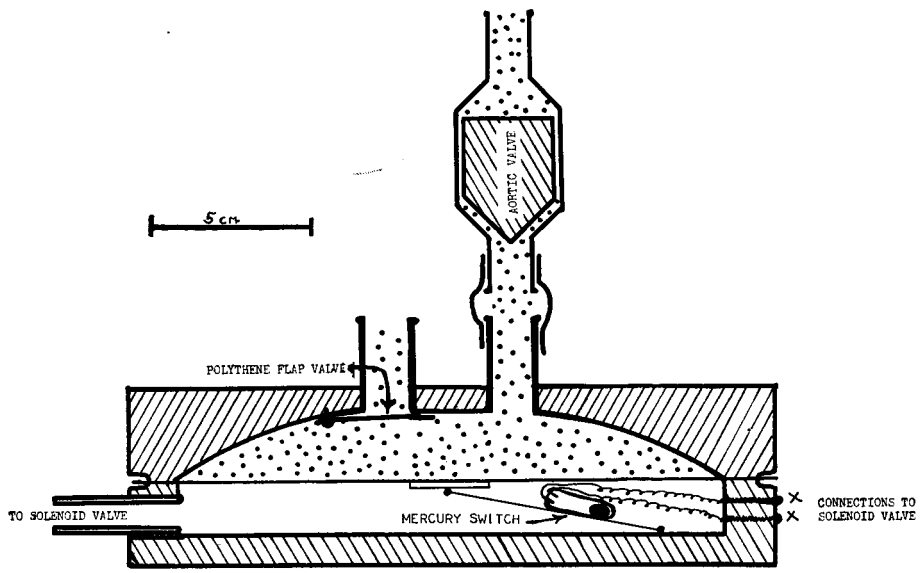

Fig. 2.—Modified Dale-Schuster pump.

The effluent from the oxygenator flows by hydrostatic pressure upward in the central chamber of the bubble trap (Fig. 1). Originally this chamber was filled with glass beads coated with Dow-Corning Anti-foam silicone, as described by Clark, Gollan, and Gupta.[13] Stainless steel scouring sponge works even more efficiently when similarly coated with Dow-Corning Anti-foam. Blood overflows from the top of the column into the outer

jacket, which serves as a reservoir, and it is led off at the bottom to the pumps. The bubble trap not only removes air bubbles but is also important in straining out strands of fibrin, should they develop.

The pumps (Fig. 2) are modified Dale-Schuster pumps[14] which are driven by compressed air. The pumping system which has been evolved is entirely self-regulating and depends for filling only on gravity. This has two important corollaries:

1. Gravity filling eliminates the negative pressure phase in the pumping cycle which was demonstrated to cause leakage of atmospheric air, through the walls of tubing which were apparently intact, into the blood stream, and which could cause effervescence of dissolved oxygen or nitrogen from the blood.

2. Each pumping cycle can be initiated only by gravity filling of the pump chamber, thus elminating the possibility of aspiration of gas from the oxygenator. This latter feature is demonstrated in Fig. 2. As the pump fills, the rubber diaphragm descends and trips a mercury switch. This causes current to flow to a solenoid valve,* which permits compressed air, at 8 to 10 pounds per square inch, to enter the space beneath the rubber diaphragm and to force the blood into the arterial circulation. In practice, only one of a pair of pumps is equipped with a mercury switch; the other pump works passively from a separate solenoid, which permits compressed air to pass when the circuit is broken.

It became apparent that opaque pump heads and opaque tubing permitted considerable amounts of air to be embolized into the arterial circulation without our having been aware of it. By reconstructing the pumps so that each pump head is made of methacrylate plastic, which is both transparent and on top of rather than beneath the blood in the pump, and by utilizing transparent polyethylene or polyvinyl tubing, we have made every part of the pumping system available for constant inspection. Blood is recirculated through a shunt from the arterial to the venous segment of the extracorporeal circuit to accomplish complete elimination of bubbles before perfusion of the subject begins. Oxygenated blood is returned by a cannula pointing centrally in one femoral artery.

In most animals it is possible to bring the clotting time back to normal by slowly giving the titrated amount of protamine, diluted with glucose or saline solution, intravenously. Too rapid administration of protamine results in temporary hypotension and a marked increase in capillary oozing from the wound. The correct dose of protamine is calculated from a heparin-protamine titration[16] at the end of perfusion. Supplemental amounts of protamine are given if the need is demonstrated by the routinely repeated protamine titrations at hourly intervals.

A transfusion of fresh whole blood, amounting to one-third the estimated blood volume, is given by transference in siliconized syringes without anticoagulants.

Chemical sterilization with 10 per cent formaldehyde solution has proved adequate for the pumps and tubing. The oxygenator is autoclaved. The entire system is primed with about 1,000 c.c. of heparinized blood (50 mg. heparin per liter).

RESULTS

For purposes of comparison, the results have been divided into three groups which roughly parallel major changes in the apparatus and in techniques.

(A) Between July 1, 1953, and July 1, 1954, total by-pass of the heart was performed in sixty-two animals with twenty survivors. Several of these animals succumbed because of errors in surgical technique, but many died from air embolism or bleeding following perfusion. These animals were perfused with the apparatus, previously described from this laboratory,[2] which had one pair of Dale-Schuster pumps for suction on the venous side and a second pair on the arterial side, and no bubble trap or filter.

*Asco Model 83143—The Automatic Switch Company, Irvington, New Jersey.

(B) Between July and November, 1954, a re-evaluation of the previous failures led to simplification of the apparatus to bare essentials: gravity drainage of venous blood, a bubble trap, and pumps which were governed entirely by venous return. The use of citrated blood for transfusion was abandoned. There were twenty-five dogs with eleven survivors. The cause of death was air embolization in three dogs, hemorrhage in ten, and pneumothorax in one.

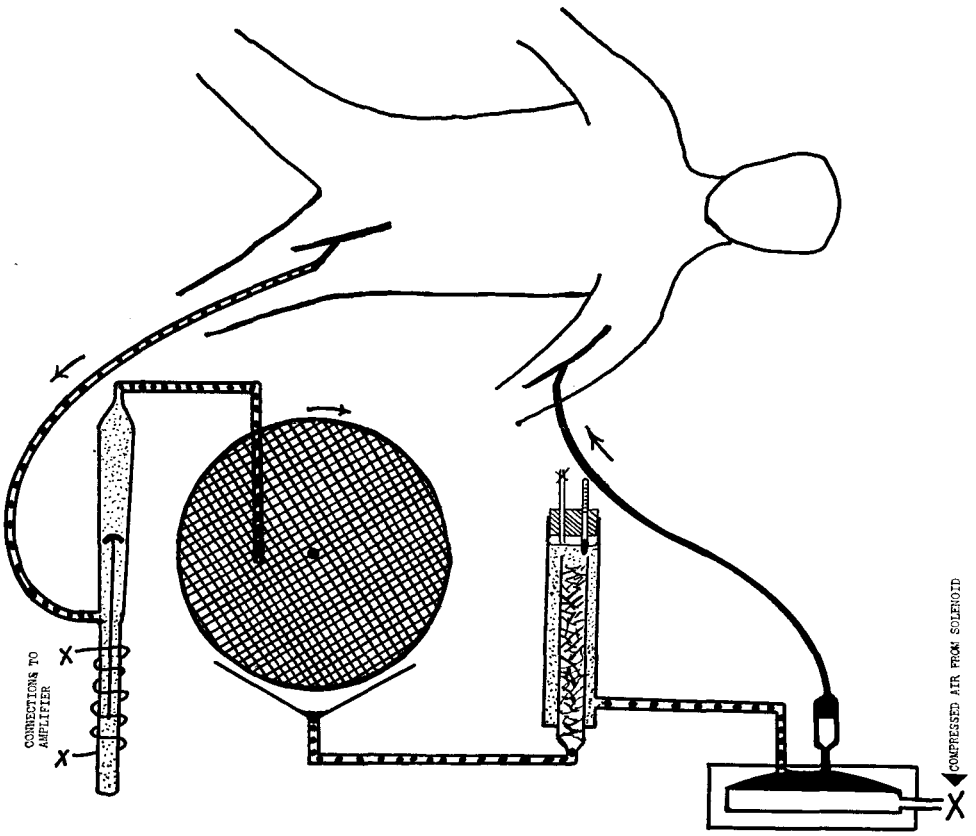

Fig. 3.—Diagram of perfusion apparatus.

(C) Between Dec. 1, 1954, and Jan. 30, 1955, twenty-four dogs were perfused and twenty-one survived. The three deaths were caused by factors not attributable to apparatus failure. One animal died because the blood remained incoagulable after heparin had been neutralized with protamine, another aspirated gastric contents during anesthesia, and the third had massive intussusception of the small bowel associated with ascaris infestation.

The average flow rate during perfusion was 700 ml. per minute, with a minimum of 375 ml. per minute in one animal, and a little over 1,200 ml. per minute in another. On a body weight basis, the flow rates were 36 ml. per kilogram per minute.

Arterial saturations during perfusion averaged 92 per cent. The arterial CO_2 fell 30 to 50 per cent below control values. This respiratory alkalosis partially counterbalanced the metabolic acidosis which all animals showed to some degree.

The oxygenator in the last two series of animals was allowed to remain at room temperature. This resulted in mild hypothermia; the average control rectal temperature was 39° C. and the average temperature after thirty minutes of perfusion was 33° C.

One patient was maintained on partial perfusion for four hours, and her history is of interest.*

Mrs. S. H., a 59-year-old housewife with known rheumatic heart disease for many years, was hospitalized at Kings County Hospital in May, 1954, with symptoms of dyspnea, orthopnea, ankle edema, and increasing fullness of the abdomen. Physical examination revealed a chronically ill woman who could not recline below an angle of forty-five degrees. The pulse was irregularly irregular with a rate of 70-90; blood pressure 140/80. Characteristic murmurs could be heard for mitral stenosis and insufficiency, aortic stenosis and insufficiency, and tricuspid insufficiency. Moist râles were present over both lungs. The liver was enlarged and tender. The abdomen showed ascites. Pitting edema of both lower extremities extended above the knees.

She was treated with digitalis, bed rest, salt restriction, and mercurial diuretics. Six months in the hospital with close medical supervision did not free her of signs and symptoms of heart failure.

On Nov. 1, 1954, she was connected to the perfusion apparatus, under sterile conditions, in the operating room. A 5 mm. polyethylene tube was inserted into the left greater saphenous vein at the fossa ovalis for withdrawal of blood from the inferior vena cava, and a 2 mm. stainless steel cannula was inserted centrally into the left brachial artery for return of oxygenated blood.

Perfusion was carried out for four hours at a rate which varied from 500 to 800 ml. per minute. The blood pressure fell from the preoperative level of 150/100 to 70/50, and then remained level at about 90 systolic. Some difficulty was experienced from severe shivering as her oral temperature fell to 31.5° C. This was controlled by warming the oxygenator until her temperature rose to about 34.5° C. and by analgesia with nitrous oxide and oxygen.

By the end of the first hour, distention of the neck veins had disappeared and pulmonary râles could no longer be heard. When she returned to her room, she was able to lie nearly flat in bed for the first time in six months. There were no neurological sequelae and no personality changes. A chest x-ray showed resorption of the hydrothorax which had been present.

Her clinical improvement lasted about ten days, and then her course was progressively downhill.

DISCUSSION

This patient is included because her problem represents one of the ways in which the apparatus can serve. It is obvious that external support for a failing circulation or acute pulmonary embarrassment (as from pulmonary edema produced by irritant gases) would be valuable. The failing circulation might result from myocardial infarction, or chronic valvular disease.

*We are indebted to Dr. William Dock and Dr. John F. Kelly of the Department of Medicine for their collaboration in treating this patient.

The marked temporary improvement in this one patient strongly suggests that the poor-risk patient with mitral stenosis might be treated by support of the circulation by the machine for several hours. After pulmonary edema has cleared, mitral valvulotomy could perhaps then be performed relatively easily. Theoretically, it should be possible to convert a Class IV patient with probable operative mortality of 40 per cent to a Class III patient who would run only a 5 to 10 per cent risk. Appropriate cases are being sought.

In this apparatus with multiple wettable surfaces, two problems arise: Fibrin formation and hemolysis. If the apparatus is to be used for partial support of the circulation for several hours, one can avoid excessive deposition of fibrin by maintaining the heparin level at 75 to 90 μg per milliliter of circulating blood (determined by protamine titration). In a 20 kilogram dog this requires a dose of heparin of 5 mg. per kilogram of body weight plus 100 mg. per liter of blood used to prime the machine. However, if perfusion is to be carried out for less than one hour, then a dose of 2.0 to 2.5 mg. of heparin per kilogram of dog, and 50 mg. of heparin per liter of blood used to prime the machine, is adequate. The usual postperfusion heparin level is then 30 to 50 μg per milliliter. These estimates of dosage and results are based upon detailed protamine titration data from 112 perfusions.

Hemolysis is not a problem. One hour of perfusion produces an average concentration of 50 mg. of free hemoglobin per 100 ml. of plasma. Even after twenty-four hours of partial perfusion, the level is only 96 mg. per cent, which from the work of Flink[15] is not high enough to initiate renal damage.

The major problem, that of hemorrhage, has been more difficult to resolve. The drawn blood of an occasional animal, after neutralization of the administered heparin by calculated amounts of protamine, forms fragile blood clots or no clots at all. Whether this is due to a fibrinolysin, to conversion of plasminogen to plasmin, to prothrombin deficiency, or to some other factor, has not been clear. Empirically, we have found that a transfusion of about one-third of the estimated blood volume in the form of fresh whole blood immediately after perfusion, will furnish any necessary clotting factors and cover any postoperative blood loss. Our losses seem to be greater than those of Gibbon[7] or of Gollan.[8]

Several metabolic problems have been investigated in the perfused dogs and will be discussed in a separate paper.

SUMMARY

1. A consistently successful method of exclusion of heart and lungs from the circulation of dogs for one-half-hour periods has been presented. Only the bronchial and coronary arterial circulations are undisturbed during perfusion.

2. Partial support of the circulation for four hours in a patient with postrheumatic trivalvular heart disease was followed by disappearance of signs of pulmonary edema and hydrothorax and by marked decrease in dyspnea and orthopnea.

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